SUBCLINICAL CAROTID ATHEROSCLEROSIS AND VITAMIN D IN PATIENTS WITH ANKYLOSING SPONDYLITIS

ANKİLOZAN SPONDİLİTLİ HASTALARDA VİTAMİN D VE SUBKLİNİK KAROTİD ATEROSKLEROZ

VITAMIN D AND ATHEROSCLEROSIS IN ANKYLOSING SPONDYLITIS

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Öz

Amaç: Karotis intima-media kalınlığı (KİMK), Ankilozan spondilit (AS) ve 25 (OH) D3 seviyesi arasındaki ilişkiyi açıklamak. Gereç ve Yöntem: Bu analizde, AS tanılı altmış üç erkek hasta ve 47 erkek kontrol değerlendirildi. AS hastalık aktivitesin değerlendirmede, Bath ankilozan spondilit hastalık aktivite indeksi (BASDAI), Bath ankilozan metrolojik indeksi (BASMI) ve Bath ankilozan spondilit fonksiyonel indeks (BASFI) skorları kullanıldı. Serum lipid düzeyleri ölçüldü. KİMK ultrasonografi ile ölçüldü. 25(OH)D3 vitamin düzeyleri ≤ 15 ng/ml Vitamin D eksikliği olarak tanımlandı. Bulgular: Hastalar ve sağlıklı kontrollerin yaş ortalaması 39,93 + 9,7 ve 40,55 + 9,7 yıl idi. Serum 25 (OH) D3 seviyesi kontrol grubu ile karşılaştırıldığında, AS'li hastalarda anlamlı derecede düşük bulundu (p = 0.034). KİMK ölçümleri kontrol grubuna göre AS grubunda yüksek bulundu, ancak istatistiksel olarak anlamlı değildi (p = 0.081). KİMK ölçümleri ile; yaş (r = 0.655, p <0.001), VKİ (r = 0.270, p = 0.033), hastalık süresi (r = 0.683, p <0.001), BASMİ (r = 0.409, p = 0.001), BASFI (r = 0,266, p = 0.035), total kolesterol düzeyleri (r = 0.290, p = 0.021) arasında pozitif korelasyon bulundu. High dansite lipoprotein düzeyleri; 25 (OH) D3>15 ng/ml olan hastalar ile karşılaştırıldığında 25 (OH) D3≤15 ng/ml hastalarda anlamlı olarak daha düşük olduğu tespit edildi (p = 0,001). Tartışma: Bu çalışmada, AS'li hastalardaki fonksiyonel ve mobilite limitasyonları ile KİMK arasındaki ilişki gösterilmiştir. Bunun yanında, D vitamini seviyesi high dansiteli lipoprotein düzeyleri ilişkilidir ve indirekt olarak aterosklerozu etkileyebilir.

Anahtar Kelimeler

Ankilozan Spondilit; Ateroskleroz; Vitamin D; BASDAI

Abstract

Aim: To clarify the associations between carotid intima-media thickness (CIMT), ankylosing spondylitis (AS), and level of 25(OH)D3. Material and Method: In this analysis, sixty-three male patients who had been diagnosed with AS and 47 male controls were evaluated. In measuring disease activity of AS, the Bath ankylosing spondylitis disease activity index (BASDAI), the Bath ankylosing spondylitis metrological index (BASMI), and the Bath ankylosing spondylitis functional index (BASFI) scores were used. Serum lipid levels were measured. CIMT was measured with ultrasonography. Vitamin D deficiency was defined as 25(OH)D3 vitamin levels ≤ 15 ng/ml. Results: The mean ages of the patients and healthy controls were 39.93+9.7 and 40.55+9.7 years respectively. Serum 25(OH)D3 levels were found to be significantly lower in AS patients as compared to the control group (p=0.034). CIMT measurements were found to be higher in the AS group than in the control group, but the difference was not statistically significant (p=0.081). CIMT measurements and age (r=0.655, p<0.001), BMI (r=0.270, p=0.033), disease duration (r=0.683, p<0.001), BASMI (r=0.409, p=0.001), BASFI (r=0.266, p=0.035), and total cholesterol levels (r=0.290, p=0.021) were found to be positively correlated. High density lipoprotein levels were also determined to be significantly lower in patients with AS levels of 25(OH)D3≤15ng/ml compared to those with levels of 25(OH)D3>15ng/ml (p=0.001). Discussion: This study showed that CIMT was associated with functional and mobility limitations in patients with AS. Also, because vitamin D level was related to high density lipoprotein levels, it may indirectly affect atherosclerosis.

Keywords

Ankylosing Spondylitis; Atherosclerosis; Vitamin D; BASDAI

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Introduction

Ankylosing spondylitis (AS), predominantly affecting young males with a peak age of onset of between 20-30 years, is an inflammatory disease of uncertain etiology which particularly affects the axial skeleton [1]. Cardiovascular involvements such as aortitis, aortic regurgitation, and conduction abnormalities are also associated with AS [2].

Chronic systemic inflammation, an underlying cause of many seemingly unrelated, age-related diseases provides a basis for the formation of atherosclerosis. Chronic inflammatory rheumatic diseases also act independently or synergistically with traditional risk factors (hypertension, hypercholesterolemia, gender, physical inactivity, smoking, etc.) in atherosclerosis [3]. Likewise, in atherosclerosis, carotid intima-media thickness (CIMT) measured with high-resolution ultrasonography is effective in predicting future cardiovascular diseases; an increased CIMT is known to indicate atherosclerotic loading [4].

Vitamin D should also be considered with regard to AS. Vitamin D has raised a great deal of interest in recent decades because of its multiple physiological functions and its significant role in the regulation of the immune system [5]. Its deficiency is an extremely common health problem that affects up to 50% of the general population [6]. Although large epidemiological studies have highlighted vitamin D deficiency as a marker of cardiovascular risk, some studies have shown that serum levels of 25(OH) D3 were not independently associated with CVD risk factors or CIMT [13-16].

The aim of this study was, first, to evaluate the association between subclinical atherosclerosis and disease activity in patients with AS. The second aim was to evaluate the impact of levels of 25(OH)D3 on the disease activity of AS. Subclinical atherosclerosis was also evaluated.

Material and Method

Participants

In this analysis, sixty-three male patients who had been diagnosed with AS and 47 healthy male controls were evaluated at the Department of Physical Therapy and Rehabilitation and Rheumatology. All AS patients were selected based on meeting the modified New York criteria [17]. The study was approved by the local ethics committee. After explaining the study procedure to each patient, written consent to participate in the study was obtained.

The patients who had a history of chronic kidney disease, myocardial infarction, percutaneous transluminal coronary angioplasty, surgery for ischemic heart disease, stroke, transient ischemic attack, carotid endarterectomy, or prior vitamin D supplementation were excluded from the study.

All patients and controls were examined by a research physician. Their ages, smoking histories, and body mass indexes (BMI) were evaluated. Some participants in this study received a diagnosis of diabetes mellitus (DM) and arterial hypertension (AH); some of them used drugs other than drugs specifically related to DM and AH. In addition to these, articular involvement extensity (only axial or both axial and peripheral), medication (only non-steroidal anti-inflammatory drugs (NSAID)/sulfasalazine and/or NSAID/biologic agents (Anti-TNF) and/or sulfasalazine and/or NSAID), and onset of first symptom and duration of disease were recorded for patients with AS.

Clinical evaluation

After the analysis using the Bath ankylosing spondylitis disease activity index (BASDAI), the Bath ankylosing spondylitis metrology index (BASMI), and the Bath ankylosing spondylitis functional index scores (BASFI) were calculated for all patients, the disease activity was assessed using the Turkish version of BASDAI, which is a self-administered questionnaire including six questions relating to symptoms of fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, and morning stiffness. It was used in accordance with the guidelines for translation of health status measures. In the first through fifth questions, patients were asked to indicate the disturbance that they had felt over the previous week on a 10 cm horizontal VAS with no distinguishing marks except the words 'easy' and 'impossible' at either ends of a line to indicate the direction of severity. Following that, in the fifth and sixth questions, morning stiffness was measured in terms of both severity and duration, respectively. The sixth question also included the duration of morning stiffness, graded every 15 minutes for two hours. Then, the mean of two scores of morning stiffness (5th and 6th questions) was calculated for data analysis. Total BASDAI score is the mean of the total of five scores with higher scores indicating higher disease activity [18].

The clinical status was evaluated using BASMI, which was calculated with the measurements of wall-to-tragus distance, lumbar flexion, cervical rotation, lumbar lateral flexion, and intermalleolar distance. Lateral flexion of the lumbar spine was measured bilaterally and the mean of right and left flexion values was accepted as a single value. Each measurement received either 0 (mild disease involvement), 1 (moderate disease involvement), or 2 (severe disease involvement) points. The sum of the five scores lies between 0 and 10, with higher scores indicating higher disease involvement.

Functional status of the patients was evaluated with BASFI. It consists of ten questions about daily activities. Each question was answered and they were scored from 0 (best possible performance) to 10 (considered the worst).

Laboratory evaluation

Following this, laboratory measurements including glucose, creatinine, ESR, CRP, lipid profile, total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), and 25(OH)D3 were determined by blood sample (fasting for at least six hours). Lipid profiles were analyzed by enzymatic techniques including nephelometry method for CRP, Westergreen method for ESR, and ELISA for 25(OH)D3. The levels of 25(OH)D3 were measured during the period from November to January. Vitamin D deficiency was defined as 25(OH)D3 serum level less than 15 ng/ml.

CIMT measurements for both groups were made by a physician without knowledge of the participants' clinical or laboratory characteristics. Measurements were made in a quiet room after 15 minutes' rest and the participants were examined in a supine position with neck extended. All bilateral common carotid artery ultrasound analyses were conducted by the same radiologist who was similarly unaware of the participants' clinical or

laboratory characteristics. Measurements were performed using a B-mode high-resolution ultrasound HD 15 (Phillips Bothel, WA, USA) with a 5-12 MHz linear probe. The distance between the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall corresponds with IMT. After localization of the common carotid artery, cross-sectional measurements were performed 10 mm proximal from the carotid bulb. While measuring, sites with mural atherosclerotic plaque were not included. For each side, three measurements were performed and a mean of each side (right or left) was calculated. Ultimately, the mean of both sides was found and plaques were defined as focal widening of the vessel wall of 50% relative to adjacent segments with protrusion into the lumen or a IMT>1.5mm.

Statistical Analysis

All data were analyzed with SPSS version 21 and expressed as the mean ± standard deviation for nominal variables and as median (min-max) for ordinal variables. Independent Samples t-test was used to test the normal distribution and homogeneity of each parameter and the Mann-Whitney U test was used to compare the data which were not normally distributed. To find out the correlations between CIMT and disease measures, the Spearman correlation coefficient test was assessed and the categorical variables (i.e. presence DM, AH) were evaluated by Chi-square tests. Statistical significance was set at p <0.05.

Results

The mean ages of the patients and healthy controls were 39.93+9.7 and 40.55+9.7 years, respectively (p=0.742). There was no significant difference in terms of BMI, smoking status, DM, or AH between patients with AS and healthy controls (p=0.528, p=0.444, p=0.293, p=0.146, respectively). Disease activity scores of patients with AS, the BASDAI (3.44+1.4), BASMI (2.6+1.9), and BASFI (2.99+1.6) were calculated (Table 1).

Table 1. The demographic characteristics of the patients with AS and healthy controls.

	Patients with AS (n=63)	Healthy controls (n=47)	P
Age (years)	39,93+9,7	40,55+9,7	0.742
BMI(kg/m2)	25,51+3,2	25,91+3,4	0.528
Smokers, n (%)	42(66,7)	28(59,6)	0,444
DM, n (%)	6(9,5)	2(4,3)	0,293
AH, n (%)	6(9,5)	9(19,1)	0,146
Age at the beginning of disease (years)	28,94+6,6		
Duration duration (years)	11+9,7		
BASDAI	3,44+1,4		
BASMI	2,6+1,9		
BASFI	2,99+1,6		

Mean+standard deviation, median (25-75 interquartile ranges)
Abbreviations: AS, Ankylosing spondylitis; BMI, Body mass İndex; DM, Diabetes mellitus; AH, Arterial hypertension; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; Bath Ankylosing Spondylitis Functional Index.

No significant difference between groups was observed in levels of HDL and ESR. CRP levels were found to be significantly higher in AS patients than in the control group (p=0.005). Serum TC, TG, and LDL levels were found to be significantly higher in the control group as compared to AS patients (p=<0.001, p=0.016, p= 0.037, respectively). Serum 25(OH)D3 levels were found to be significantly lower in AS patients as compared to the control group (p=0.034). CIMT measurements were found to be higher in the AS group than in the control group, but this was not statistically significant (p=0.081) (Table 2).

Table 2. The laboratory measures of the patients with AS and healthy controls.

	Patients with AS (n=63)	Healthy controls (n=47)	p
ESR (mm/h)	16,28+12,8	11,83+7,1	0,223
CRP (mg/L)	1,46+2,4	0,52+0,2	0,005
TC (mg/dl)	174,52+35,7	203,32+33,9	<0,001
TG (mg/dl)	131,19+104,2	139,74+48,7	0,016
HDL (mg/dl)	43,06+8,5	45,66+8,9	0,123
LDL (mg/dl)	102,82+22,6	113,57+30,9	0,037
25(OH)D3 (ng/ml)	15,60+5,8	20+8,2	0,034
CIMT (mm)	0,66+0,2	0,61+0,2	0,081

Mean+standard deviation, median (25-75 interquartile ranges)
Abbreviations: AS, Ankylosing spondylitis; ESR, Erythrocyte sedimentation rate; CRP: C-reactive protein; TC, Total cholesterol; TG, Tryglicerides; HDL, High density lipoprotein; LDL, Low density lipoprotein; CIMT, Carotid intima-media thickness.

In Table 3, medications for both groups are reported.

Table 3. The medications use of patients with AS and healthy controls.

	Patients with AS (n=63)	Healthy controls (n=47)
NSAID, n (%)	57(90,5)	
Sulfasalazine, n (%)	29(46)	
Glucocorticoid, n (%)	-	
Anti-TNF, n (%)	14(22,2)	
Methotrexate, n (%)	2(3,2)	
Antihypertensive drugs, n (%)	-	6(12,8)
Antidiabetic drugs, n (%)	6(%9,5)	

Abbreviations: AS, Ankylosing spondylitis; NSAID, Non-Steroidal Anti-Inflammatory Drug;

CIMT measurements and age (r= 0.655, p<0.001), BMI (r=0.270, p=0.033), disease duration (r=0.683, p<0.001), BASMI (r=0.409, p=0.001), BASFI (r=0.266, p=0.035), and TC (r=0.290, p=0.021) were found to be positively correlated (Table 4).

There was no difference in CIMT, BASDADI, BASMI, BASFI between patients with vitamin D deficiency (≤15ng/ml) and those without (>15ng/ml). However, HDL levels were determined to be significantly lower in patients with AS levels of 25(OH) D3≤15ng/ml (p=0.001) (Table 5).

Discussion

In this study, first, the association between subclinical atherosclerosis and disease activity in patients with AS was evaluated. Secondly, the impacts of the levels of 25(OH)D3 on the disease activity of AS and subclinical atherosclerosis were evaluated. Results found in this study indicate that when compared to healthy controls, CIMT measurements were higher in AS patients, but not at the level of statistical significance.

When 25(OH)D3 levels were investigated, AS patients were

Table 4. Correlation between carotid intima-media thickness measurements and demographic, clinical, laboratory parameters in AS patients.

	Correlation coefficient	P
Age (years)	0,655	<0,001
BMI(kg/m2)	0,270	0,033
Age at the beginning of disease (years)	0,056	0,664
Disease duration (years)	0,683	<0,001
BASDAI	0,115	0,367
BASMI	0,409	0,001
BASFI	0,266	0,035
ESR (mm/h)	0,174	0,173
CRP (mg/L)	0,147	0,249
TC (mg/dl)	0,290	0,021
TG (mg/dl)	0,188	0,141
HDL (mg/dl)	0,042	0,745
LDL (mg/dl)	0,143	0,265
25(OH)D3	0,138	0,279

Abbreviations: AS, Ankylosing spondylitis; BMI, Body mass İndex; DM, Diabetes mellitus; AH, Arterial hypertension; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; Bath Ankylosing Spondylitis Functional Index; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; TC, Total cholesterol; TG, Tryglicerides; HDL, High density lipoprotein; LDL, Low density lipoprotein.

Table 5. Association between 25(OH)D3 and CIMT and disease activity index, serum lipid levels in AS patients.

	25(OH)D3 (ng/ml)		P
	≤15ng/ml	>15ng/ml	
	n=34	n=29	
BASDAI	3,22±1,22	3,68±1,5	0,114
BASMI	2,41±1,84	2,82±2	0,303
BASFI	2,85±1,5	3,14±1,8	0,443
CIMT (mm)	0,65±0,2	0,66±0,2	0,786
TC (mg/dl)	185,3±41,3	188,15±34,5	0,364
TG (mg/dl)	144,53±112,7	126,47±49,1	0,957
HDL (mg/dl)	41,22±7,7	46,72±8,8	0,001
LDL (mg/dl)	109,02±28,2	106,03±25,7	0,688

Mean+standard deviation, median (25-75 interquartile ranges)
Abbreviations: Abbreviations: AS, Ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; Bath Ankylosing Spondylitis Functional Index; CIMT, Carotid intima-media thickness; TC, Total cholesterol; TG, Tryglicerides; HDL, High density lipoprotein; LDL, Low density lipoprotein.

found to have lower levels than healthy controls. Age, BMI, disease duration, BASMI, BASFI, and TC were also found to be positively correlated with CIMT measurements. Although 25(OH) D3 levels and HDL levels were determined to be positively correlated, 25(OH)D3 levels and BMI were negatively correlated.

In regard to subclinical atherosclerosis and AS, studies in the literature are reported significantly conflicting results. In the study carried out by Perrotta et al. it was demonstrated that carotid bulb IMT, a morphological index of subclinical atherosclerosis, was found to be higher in controls than in AS patients without risk factors for cardiovascular disease. However, this could be influenced by the small number of study participants (20 AS patients and 20 healthy controls) [19].

The studies involving patients with a BASDAI > 4 demonstrated that patients with AS had a higher CIMT than those of the control group [20-22]. A recent study by Berg et al. examining the association between disease activity in AS and markers of vascular pathology concluded that the patients with high AS disease activity had a higher cardiovascular disease risk. However, this finding might be the result of the mean age of the study participants (approximately 50 years) [23]. One of the other recent studies published by the same researchers in which possible factors of cardiovascular risks were evaluated supported the conclusion that disease activity was related to elevated arterial stiffness and the future risk of cardiovascular disease [24].

However, a cross-sectional study showed that CIMT and parameters related to arterial elastic properties in young AS patients without clinically evident cardiovascular risk factors were not different from those of sex- and age-matched healthy controls. In the study, disease duration and the disease activity index of patients with AS were low [25]. Mathieu et al. also found no statistically significant differences between CIMT values in sixty patients with AS and age/sex-matched controls [26].

A meta-analysis performed on studies published up to 2009 concluded that atherosclerosis was accelerated in patients with AS, as evidenced by significantly greater CIMT values compared with controls [27]. However, six subsequently published original case-control studies have shown that CIMT in AS was not found to be higher [29, 33]. It has been reported that in patients with high disease activity with a mean age of more than 50 years, carotid plaques were significantly more prevalent than in controls [34]. In the literature, other studies have also observed higher CIMT in AS patients compared to a control group, but the results were not statistically significant [35, 36].

Arida et al. concluded that in patients with AS with low disease activity, subclinical atherosclerosis was not accelerated compared with healthy individuals. However, the findings of Arida et al. cannot be directly compared with those of previous studies, because none of them consisted of a strict 1:1 matching for each of the classical CVD risk factors [37]. Of significance, meta-analysis of Arida et al. confirmed original data because the subgroup analysis of studies involving patients with a BASDAI < 4 showed that CIMT was similar to controls. As expected, overall and subgroup meta-analysis revealed that active AS disease was indeed associated with increased CIMT. However, the presence of increased IMT does not show increased atheromatosis; it may also be attributed to subclinical vasculitis and/or wall hypertrophy. The absence of increased CIMT in patients with AS with low disease activity could also be associated with the resolution of vessel wall inflammation [37]. In our study, it is clear that subclinical atherosclerosis is not accelerated in patients with AS with low disease activity (BASDAI < 4). These results may be due to the younger patients with AS in our study (approximately 40 years). Also, serum TC, TG, and LDL levels were higher in the control group as compared to the AS group. The increase in the elevation of serum lipid levels in the control group may be due to CIMT measurements.

Hamdi et al. found that AS was associated with an increase in risk for atherosclerosis, independent of traditional risk factors. Disease activity, functional and mobility limitations, structural damage, and inflammation were found to be the most incriminated risk factors [38]. In our study, CIMT measurements and age, BMI, disease duration, BASMI, and BASFI were positively correlated and our results showed that functional and mobility

limitations in AS patients are related to the risk of atherosclerosis.

In a case study only evaluating the relationship of vitamin D and AS, significant correlations between serum 25(OH)D3 levels and AS activity were not found [7], whereas inconsistent conclusions were obtained in some studies in which different testing tools were used [8, 9, 11]. In addition, a meta-analysis revealed that 25(OH)D3 was associated with AS susceptibility and there was a consistent and inverse relationship between serum vitamin D levels and AS activity [39]. In our study, serum 25(OH) D3 levels were found to be significantly lower in AS patients as compared to the control group, but significant correlations between serum 25(OH)D3 levels and disease activity of AS were not demonstrated.

The results of the previous studies in the literature on this topic are highly controversial. In large epidemiological studies, vitamin D deficiency has been emphasized as a marker of cardiovascular risk that promotes accelerated atherosclerosis and subsequent cardiovascular events [13, 40-42]. In contrast, serum levels of 25(OH)D3 were not found to be independently associated with CVD risk factors or CIMT in some studies [14-16]. Vitamin D also has been shown to have some anti-atherogenic functions, inhibiting the formation of foam cells, cholesterol uptake by the macrophages, and enabling HDL transport [43]. Lower serum 25-hydroxyvitamin D had a relation with metabolic syndrome and its components, especially HDL cholesterol concentration [44]. In our study, HDL levels were significantly lower in AS patients with levels of 25(OH)D3≤15ng/ml and HDL levels and vitamin D were positively correlated (r=0.302, p=0.001).

The CARMA study describes a positive association with 25(OH) D3 deficiency in the patients with chronic inflammatory rheumatic diseases (rheumatoid arthritis, AS, and psoriatic arthritis) when compared with the non-chronic inflammatory rheumatic diseases subjects. In a 10-year prospective study that evaluated the risk of cardiovascular events, a positive association was not statistically significant for AS. However, no radiographic measurement method was used to evaluate atherosclerosis [37]. In our study, although serum vitamin D levels were found to be significantly lower in AS patients as compared to the control group, vitamin D deficiency was not correlated with CIMT, BASDADI, BASMI, or BASFI in patients with AS. Vitamin D deficiency was correlated with HDL level in patients with AS.

There are several limitations in the present study. The number of participants in the study group was relatively small. Our study may design between patients with AS with low disease activity (BASDAI < 4), high disease activity (BASDAI > 4), and control.

In addition to all these, many factors can affect CIMT (i.e., traditional cardiovascular risk factors such as age, sex, race, smoking, alcohol consumption, immunological diseases, and vitamin D). The present study looked at the connection between AS and vitamin D deficiency. However, we evaluated the relation between AS and vitamin D with CIMT. Although 25(OH)D3 levels were found to be lower in AS patients, disease activity did not appear to have been a factor. On the contrary, Vitamin D level was related to high density lipoprotein levels and it affected atherosclerosis indirectly. Age, BMI, disease duration, BASMI, BASFI, and TC were also found to be positively correlated with CIMT measurements. Chronic inflammatory rheumatic diseases act independently or synergistically with traditional risk factors (hypertension, hypercholesterolemia, and physical inactivity, obesity, etc.) in atherosclerosis [3]. The findings of the present study, in which the relationship between CIMT with ankylosing spondylitis and 25(OH)D3 was studied, need to be confirmed in further studies.

Competing interests

The authors declare that they have no competing interests.

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